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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,591	11/14/2003	Janakiraman Ramachandran	021958-001410US	3234

20350 7590 10/12/2007

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EXAMINER	
KINSEY, NICOLE	

ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
10/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,591	RAMACHANDRAN ET AL.	
	Examiner	Art Unit	
	Nicole E. Kinsey, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *1-9 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-13 and 17-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-29 are pending. Claims 1-9 and 14-16 are withdrawn from consideration, and claims 10-13 and 17-29 are under examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10 and 17-21 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson-Boaz et al.

Johnson-Boaz et al. describes the production and isolation of bacteriophages (λrj1) that have a mutation in the holin or S gene (i.e., holin-modified). The phages are

isolated in buffer or water (see Experimental Procedures, pages 502-503). In addition, the phages cause early lysis in the host, thus inactivating the host and producing extremely low titers of phage progeny (page 497, Isolation of the early-lysis mutant). Because the phage of Johnson-Boaz et al. has the same characteristics as applicants' phage (i.e., early lysis of bacteria and reduced production of phage progeny), one would reasonably expect the phage to have a reduced effect on the host's immune system (i.e., reduced anti-phage immune response).

Claims 17 and 22 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson-Boaz et al. and Ghanbari et al. (U.S. Patent No. 6,121,036).

The disclosure of Johnson-Boaz et al. is discussed above. Johnson-Boaz et al. does not specifically contemplate a composition comprising both phage and an antibiotic. However, Ghanbari et al. teaches compositions of phage and antibiotics to treat bacterial infections (see, for example, the abstract).

It would have been obvious to one of skill in the art to combine the phage and antibiotic in the generation of an anti-bacterial composition. One of ordinary skill in the art would have been motivated to make the claimed composition as both phage and antibiotics are known anti-bacterial agents (see Ghanbari et al.). One of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed composition for the intended use of inhibiting or killing bacteria.

Further, the courts have said: "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose,

in order to form a third composition to be used for the very same purpose . . . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious.) See MPEP 2144.06. In this case, applicants are combining two known anti-bacterial agents.

Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 10-13, 28 and 29 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson-Boaz et al. in view of Taylor et al. (U.S. Patent No. 2,851,006) and Clark.

The disclosure of Johnson-Boaz et al. is discussed above. Johnson-Boaz et al. does not teach a lyophilized form of phage or a composition of two or more different holin-modified bacteriophage that effect inhibition of at least two different bacterial hosts.

Clark discloses lyophilized phage preparations that contained viable phage.

It would have been obvious to one of ordinary skill in the art to lyophilize a phage preparation for storage purposes as taught by Clark. One would have been motivated to do so, given the suggestion by Clark that lyophilization is a very convenient method for preserving phage. There would have been a reasonable expectation of success,

given the fact that it is well known in the art that lyophilization is commonly used to preserve microorganisms. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

With regard to a two-phage composition, it is well known in the art that compositions containing more than one different phage, each specific for a different host, will provide broader bactericidal effects. For example, Taylor et al. teaches that cocktails of phages should be used to assure the destruction of all possible species of contaminating bacteria, namely Salmonella (col. 2, lines 25-44). Thus, it would have been obvious for one of ordinary skill in the art to combine two or more different phages in a composition as suggested by Taylor et al. against contaminating bacteria (e.g., known pathogens such as Salmonella, E. coli, Pseudomonas, etc.). There would have been a reasonable expectation of success given the knowledge that phages kill bacteria and also given the knowledge that more than one strain or species of bacteria can contaminate/infect an object or individual. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 10 and 23-27 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson-Boaz et al. in view of Vukov et al. (FEMS Microbiology Letters, 2000, 184, 179-186).

The disclosure of Johnson-Boaz et al. is discussed above. Johnson-Boaz et al. does not teach a holin-modified phage comprising a non-endogenous holin gene operably linked to a promoter (or an inducible promoter) that facilitates early expression.

Vukov et al. discloses the functional analysis of heterologous holin genes in a λΔS background. The recombinant phage comprise holin genes expressed under the control of a heterologous promoter. Vukov et al. is cited for its teaching that holin genes can be placed in various phage backgrounds to evaluate the ability to support lysis on *E. coli*. Further, Vukov et al. was cited for its teaching that heterologous promoters can be used to express holin genes.

Therefore, taking the combined teachings of Johnson-Boaz et al. and Vukov et al., it would have been obvious to one of ordinary skill in the art to modify the phage of Johnson-Boaz et al. to produce recombinant phage with exogenous holin genes as taught by Vukov et al. One would have been motivated to do so given the suggestion by Vukov et al. that recombinant holin phage expressing heterologous holin genes can allow for the qualitative evaluation of the ability of the heterologous holin to support lysis of particular bacteria, such as E. coli, and that recombinant holin phage can be used to determine lysis timing for holin gene products from various phage (see, for example, the abstract and discussion). There would have been a reasonable expectation of success given the fact that Vukov et al. successfully produced recombinant phage with heterologous holin genes. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

With regard to promoter choice (claims 23, 25, and 26), the choice of promoter (e.g., prokaryotic, eukaryotic, inducible, etc.) is well within the purview of the ordinary skilled artisan. Therefore, it would have been obvious to select an inducible promoter or a promoter that facilitates early expression. For example, to control the expression of a

holin protein, one would select an inducible promoter. Further, to characterize a holin protein or to raise antibodies against a holin protein, one would select a promoter to express the holin protein, preferably the CMV promoter as it is known in the art to yield high levels of protein. Therefore, choosing a particular promoter to link to the holin protein is routine.

Response to Arguments

Applicants' arguments filed July 30, 2007 have been fully considered but they are not persuasive.

In the reply dated July 30, 2007, applicants argue that claim 10 specifies that the holin-modified phage is administered in a pharmaceutically acceptable carrier and that the utility of the claimed phage composition is different from the utility of the phage compositions of Johnson-Boaz et al.

This argument is not found persuasive. The claims are directed to a composition comprising a holin-modified phage and a pharmaceutically acceptable carrier. The claimed composition is suitable for administration to an infected mammal and the phage is characterized by i) early lysis and ii) reduced anti-phage immune response.

Johnson-Boaz et al. discloses what applicants claim. Johnson-Boaz et. describes the production and isolation of bacteriophages (λrj1) that have a mutation in the holin or S gene (i.e., holin-modified). The phages are isolated in buffer or water (see Experimental Procedures, pages 502-503, especially page 502, right column). Thus, the composition of Johnson-Boaz et al. is suitable for administration to an infected

mammal. In addition, the phages cause early lysis in the host, thus inactivating the host and producing extremely low titers of phage progeny (page 497, Isolation of the early-lysis mutant). Because the phage of Johnson-Boaz et al. has the same characteristics as applicants' phage (i.e., early lysis of bacteria and reduced production of phage progeny), one would reasonably expect the phage to have a reduced effect on the host's immune system (i.e., reduced anti-phage immune response).

Furthermore, applicants have merely further purified a known product. According to section 2144.04 (VII) of the MPEP, pure materials are novel *vis- à-vis* less pure or impure materials because there is a difference between pure and impure materials. Therefore, the issue is whether claims to a pure material are unobvious over the prior art. In re Bergstrom, 427 F.2d 1394, 166 USPQ 256 (CCPA 1970). **Purer forms of known products may be patentable, but the mere purity of a product, by itself, does not render the product unobvious**. Ex parte Gray, 10 USPQ2d 1922 (Bd. Pat. App. & Inter. 1989) (emphasis added).

Factors to be considered in determining whether a purified form of an old product is obvious over the prior art include whether the claimed chemical compound or composition has the same utility as closely related materials in the prior art, and whether the prior art suggests the particular form or structure of the claimed material or suitable methods of obtaining that form or structure. In re Cofer, 354 F.2d 664, 148 USPQ 268 (CCPA 1966) (Claims to the free-flowing crystalline form of a compound were held unobvious over references disclosing the viscous liquid form of the same compound because the prior art of record did not suggest the claimed compound in

crystalline form or how to obtain such crystals.). See also Ex parte Stern, 13 USPQ2d 1379 (Bd. Pat. App. & Inter. 1987) (Claims to interleukin 2 (a protein with a molecular weight of over 12,000) purified to homogeneity were held unpatentable over references which recognized the desirability of purifying interleukin 2 to homogeneity in a view of a reference which taught a method of purifying proteins having molecular weights in excess of 12,000 to homogeneity wherein the prior art method was similar to the method disclosed by appellant for purifying interleukin 2.).

Here, the claimed pharmaceutical phage composition has the same utility and characteristics as the phage composition of Johnson-Boaz et al. Both compositions have phage with a mutated or modified holin gene that results in early lysis in the host, thus inactivating the host and producing extremely low titers of phage progeny. Further, Johnson-Boaz et al. describes suitable methods of obtaining the holin-modified phage. Therefore, applicants' purified pharmaceutical form of a known holin-modified phage is obvious over the prior art.

Applicants' argument that the utility of the claimed holin-modified phage versus the utility of the missense mutation in the holin gene of the Johnson-Boaz et al. phage is different implies that the missense mutation of Johnson-Boaz et al. would not be an effective composition (i.e., not enabled for applicants claimed invention). However, applicants' claims encompass the phage composition of Johnson-Boaz et al. as outlined above. Therefore, applicants' argument can be construed as an admission that the full scope of applicants' claims is not enabled.

Applicants next argue that Johnson-Boaz et al. does not suggest that the composition is at least 60% by weight free from proteins and naturally-occurring organic molecules. This, too, is not found persuasive. Johnson-Boaz et al. discloses a phage composition where the phage is treated with $CHCl_3$, vortexed, and then centrifuged to clear cell debris. The cleared composition was then used in tittering assays (see page 502, right column).

Applicants next argue that the phage of Johnson-Boaz et al. exhibits early lysis at 42°C, a temperature above that maintained by most mammals. This argument is not found persuasive because Table 3 of Johnson-Boaz et al. (page 500) clearly shows early lysis (approximately 18 minutes) for the holin-modified phage at 30°C, 37°C and 42°C and significantly reduced particle burst at each temperature.

With regard to the rejection of claims 17 and 22 under 35 U.S.C. 103(a) as being unpatentable over Johnson-Boaz et al. and Ghanbari et al. (U.S. Patent No. 6,121,036), applicants argue that Ghanbari et al. was cited merely for its alleged teaching of methods of preparing a purified, toxin-free phage preparation. This is not correct. Ghanbari et al. teaches the claimed composition. Column 3, lines 49-65, states that the phage preparations of the invention preferably can be used in combination with known antibiotics such as aminoglycosides, cephalosporins, macrolides, erythromycin, monobactams, penicillins, quinolones, sulfonamides, tetracycline, and various anti-infective agents. For example, a phage preparation effective against various strains of staphylococcus could be used in combination with a cephalosporin such as Keflex or Keftab (both from Cephalexin). The combination of Ghanbari et al. can be used to treat

specific bacterial infections. Particularly effective in this regard are phage preparations which act by killing the microorganism, and which act on specific infections by obliterating sufficient numbers of the microorganisms present in the infectious focus (see col. 6, lines 20-27).

Therefore, for the reasons outlined above, applicants' invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made.

No claim is allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nicole E. Kinsey, Ph.D. whose telephone number is

(571) 272-9943. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nicole E. Kinsey, Ph.D.
Examiner
Art Unit 1648

/nk/

/Stacy B. Chen/ 10-10-07
Primary Examiner, TC1600